American Society of Hematology, 52nd Annual Meeting and Exposition

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More than 18,000 physicians and other medical specialists from more than 100 countries attended the premier hematology conference in Orlando, Fla., from December 4 to 7, 2010. Approximately 4,500 attendees arrived from countries outside the U.S. This month's column presents high-interest sessions on leukemias, multiple myeloma, and other hematological malignancies.

Dasatinib (Sprycel) Versus Imatinib (Gleevec) In Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia: The DASISION Trial, 18-Month Follow-up

- Neil Shah, MD, PhD, University of California, San Francisco School of Medicine, San Francisco, Calif.

Compared with imatinib (Gleevec, Novartis), dasatinib (Sprycel, Bristol-Myers Squibb) 100 mg resulted in higher and faster rates of complete cytogenetic responses (CCyRs) and major molecular response (MMRs) in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML–CP). The findings emerged from a longer-term, 14-month follow-up of the DASISION (*Das*atinib versus *I*matinib *S*tudy *i*n Treatment-Naive CP–CML Patients) trial.

In DASISION, 519 patients who were treated at 108 centers in 26 countries were randomly assigned to receive either dasatinib 100 mg once daily (n = 259) or imatinib 400 mg once daily (n = 260). The primary endpoint was confirmed CCyRs by 12 months.

Confirmed CCyR rates, which had significantly favored dasatinib 100 mg daily over imatinib 400 daily mg (77% vs. 67%; $P = 0.0086$) at 12 months, continued to favor dasatinib 100 mg daily (78% vs. 70%; $P = 0.0366$). The likelihood of achieving a CCyR at any time was 1.5-fold higher with dasatinib than with imatinib ($P < 0.0001$). Among patients who achieved CCyRs, the median times to CCyRs were 3.1 months for dasatinib and 5.8 months for imatinib.

In addition, more dasatinib patients achieved the higher standard of MMRs (*bcr-abl* ≤ 0.0032%). MMRs were 1.8-fold more likely with dasatinib than with imatinib ($P < 0.0001$). Among patients achieving MMRs, the median times to MMRs were 8.3 months for dasatinib and 11.8 months for imatinib.

Progression to advanced-phase CML was experienced by six of 259 of patients (2.3%) receiving dasatinib and by nine of 260 patients (3.5%) receiving imatinib. No patients who achieved MMRs have shown progression to the accelerated or blast phase to date, Dr. Shah said.

Overall, discontinuations of therapy were similar between groups (dasatinib, 19%; imatinib, 20%). Fluid retention, superficial edema, myalgia, and nausea were more common with imatinib, whereas pleural effusion (all grades, 12% vs. 0%, respectively) and thrombocytopenia (grade 3 or 4, 19% vs. 10%, respectively) were more common with dasatinib. Four dasatinib patients (1.5%) discontinued therapy because of pleural effusions.

"Longer follow-up continues to support the use of dasatinib 100 mg once daily as first-line treatment for newly diagnosed CML–CP," Dr. Shah concluded.

Nilotinib (Tasigna) Found Superior to Imatinib (Gleevec) in Chronic-Phase Chronic Myeloid Leukemia: ENESTnd Update

- Timothy P. Hughes, MD, Department of Hematology, Royal Adelaide Hospital, Adelaide, Australia

ENESTnd (*E*valuating *N*ilotinib *E*fficacy and *S*afety in Clinical *T*rials in *N*ewly *D*iagnosed Patients) is a global, multicenter, randomized phase 3 study. Conducted at 217 centers in 35 countries, this study is comparing nilotinib (Tasigna, Novartis) with imatinib (Gleevec, Novartis) in patients with newly diagnosed CML–CP.

At 24 months, among patients receiving nilotinib 300 mg twice daily (n = 282) and nilotinib 400 mg (n = 281), 74% and 78%, respectively, continued with treatment; 67% of patents in the imatinib 400 mg once-daily group (n = 283) continued with treatment. Discontinuation rates attributed to disease progression were reported to be less than 1% for nilotinib 300 mg twice daily, 1% for nilotinib 400 mg twice daily, and 4% for imatinib 400 mg once daily.

Discontinuations for suboptimal response or treatment failure were higher for nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib 400 mg once daily, reported at 9%, 2%, and 13% across the respective treatment arms. Death rates were 1% with nilotinib 300 mg twice daily, less than 1% with nilotinib 400 mg twice daily, and 0% for imatinib 400 mg once daily.

Between 12 and 24 months, rates of MMRs increased in all treatment groups. At 12 months, significantly higher MMR proportions noted in the nilotinib arms (44%, 43%), compared with imatinib (22%) ($P < 0.0001$ for both), were sustained at 24 months (62% and 59% with nilotinib vs. 37% with imatinib; $P < 0.0001$ for both). Fewer than 2% of patients in each treatment arm failed to maintain their MMRs between 12 and 24 months.

Comparing kinetics of molecular responses (MRs), Dr. Hughes noted that specific depths of *bcr-abl* transcript reductions typically occurred 12 months sooner in the nilotinib arms than in the imatinib arm. The percentages of patients achieving 4-log reductions in *bcr-abl* (complete MRs [CMRs[4]]) at

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any time were 44% with nilotinib 300 mg, 36% with nilotinib 400 mg, and 20% with imatinib 400 mg, and 4.5 log reductions ($CMR^{4.5}$) were 26%, 21%, and 10%, respectively. All differences between the nilotinib arms and the imatinib arm were highly significant. By 24 months, rates of complete cytogenetic responses (CCyRs) were as follows:

- 87% for nilotinib 300 mg twice daily ($P = 0.0018$) vs. imatinib 400 mg once daily
- 85% for nilotinib 400 mg twice daily ($P = 0.016$) vs. imatinib 400 mg once daily
- 77% for imatinib 400 mg once daily

Progression to the accelerated or blast phase was significantly more frequent in the imatinib 400-mg patients (4.2%) than in the nilotinib 300-mg and 400-mg arms (0.7% and 1.1%, respectively; $P = 0.0059$ and $P = 0.0196$, respectively).

Both nilotinib doses were generally well tolerated, but there were fewer discontinuations related to adverse events with the 300-mg twice-daily dose. Nausea, diarrhea, and vomiting were more common with imatinib; the incidence of rash, headache, pruritus, and alopecia was higher in the nilotinib arms.

"Longer follow-up supports the superiority of nilotinib for the treatment of patients with newly diagnosed CML–CP," Dr. Hughes concluded.

Pralatrexate (Fotolyn) in Cutaneous T-Cell Lymphoma: A Dose-Finding Study

• Steven M. Horwitz, MD, Memorial Sloan Kettering Cancer Center, New York, N.Y.

Response rates in advanced relapsed or refractory cutaneous T-cell lymphoma (CTCL) with systemic therapies have usually been in the vicinity of 30% (range, from 30% to 54% overall), and durable remissions are uncommon when patients are not receiving therapy. In a study aimed at finding a better and safer schedule with pralatrexate injection (Folotyn, Allos) for this population, a response rate of 61% was achieved among patients receiving the intended dose intensity of 15 mg/m^2 or higher weekly for three to four weeks. The weekly response rate for a lower-dose intensity (of 15 mg/m^2 or less) for two to three weeks was 8%. Some responses were observed at all dose levels.

The starting dose of pralatrexate was 30 mg/m^2 weekly for three to four weeks by intravenous (IV) push over three to five minutes. Toxicities, however, led investigators to reduce the dose to 20, 15, and 10 mg/m^2 with schedules of three to four weeks or two to three weeks. All patients received supplementation with intramuscular (IM) vitamin B_{12} 1 mg every eight to 10 weeks and oral folic acid 1 mg/day.

Among 54 treated patients, 59% were male; the median age was 61.5 years. The median number of previous systemic therapies was 4 (range, 1–11). Dr. Horwitz reported that in a second stage of evaluation among 29 patients receiving the optimal dose, the response rate was 45%; one patient achieved a complete remission (CR), and 12 patients achieved partial remissions (PRs). The overall response rate was 41% for the 54 evaluable patients, including three CRs and 19 PRs. The median duration of response was not reached (range, 1–372 days). Kaplan–Meier estimates showed a six-month response rate of 73%.

The most common adverse event was stomatitis, reported in 48% of patients, but most occurrences were grade 1 or 2 (in 31%).

"Further research is warranted to confirm these data and to evaluate pralatrexate in earlier lines of therapy in CTCL and in combination with other active therapeutics," Dr. Horwitz concluded.

Zoledronic Acid (Zometa) Plus Thalidomide Combinations Achieve Improved Survival In Multiple Myeloma: The MRC Myeloma IX Trial

• Gareth J. Morgan, PhD, Institute of Cancer Research, The Royal Marsden National Health Service Foundation Trust, London, U.K.

In previous research by Dr. Morgan, zoledronic acid (Zometa, Novartis) resulted in a reduction of skeletal-related events (SREs), such as fractures, and improved overall survival; however, the overall survival benefit was independent of the SRE effect, suggesting anti-myeloma activity. Dr. Morgan's earlier studies had also shown the superiority of thalidomide-containing induction regimens for multiple myeloma (MM).

The Medical Research Council (MRC) Myeloma IX trial, conducted at 121 centers, enrolled 1,960 patients with newly diagnosed stage I–III MM. Both intensive and non-intensive regimens were explored.

In the intensive regimen, 1,111 patients were randomly assigned to receive four to six three-week cycles of chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) or cyclophosphamide, thalidomide, and dexamethasone (CTD) as induction therapy, followed by high-dose melphalan (e.g., Alkeran, GlaxoSmithKline) and autologous stem-cell transplantation.

With the non-intensive pathway, patients were randomly assigned to receive four-week cycles of melphalan plus prednisolone or attenuated CTD (CTDa). Each treatment arm also received zoledronic acid 4 mg IV every three to four weeks—with the dose adjusted based on renal function (n = 981)—or the bisphosphonate clodronic acid (clodronate 1,600 mg/day) (n = 979). This regimen was continued at least until disease progression.

Primary endpoints for zoledronic acid (n = 981) versus clodronate (n = 979) comparisons were progression-free survival, overall survival, and patient responses. SREs (fracture, spinal cord compression, radiation or surgery to bone, and new osteolytic lesions at disease progression) constituted a secondary endpoint.

Mean age was 59.5 years (38% female), and mean follow-up was 3.8 years. Disease progression or death was reported in 59.2% of patients in the zoledronic acid group and in 63.9% of the clodronate group. Zoledronic acid significantly extended overall survival by 5.5 months, compared with clodronate ($P = 0.04$) and reduced the risk of death by 16%. Zoledronic acid also improved progression-free survival by 12%, compared with clodronate ($P = 0.0179$).

The highest rate of complete responses (CRs) and very

good partial responses (VGPRs) was reported for thalidomide-containing regimens with zoledronic acid in both the intensive pathway (CTD, 45.1% vs. 41.4%; *P* not significant) and in the non-intensive pathway (CTDa) (34% for zoledronic acid, 26% for clodronate; $P = 0.11$).

SREs were significantly reduced with zoledronic acid (27%), compared with clodronate (35.3%) ($P = 0.0004$) overall and in non-intensive and intensive pathways.

Confirmed osteonecrosis of the jaw was higher with zoledronic acid (4%) than with clodronate (1%) ($P = 0.0037$).

"Adding zoledronic acid to novel agents reduces bone disease and may correlate with better response and survival," Dr. Morgan concluded.

Lenalidomide (Revlimid) Maintenance Therapy For Multiple Myeloma After Transplantation: The IFM 2005-02 Trial, Final Analysis

- Michel Attal, MD, Hopital Purpan, Toulouse, France

Effective maintenance therapy is necessary in multiple myeloma (MM) after single or double transplantation because the residual disease that causes relapse is always present. Experience has shown chemotherapy to be ineffective and interferon's benefit to be marginal, and the role of steroids remains controversial, said Dr. Attal. Whether lenalidomide (Revlimid, Celgene), an analogue of thalidomide without thalidomide's neurological toxicity, is a promising option was tested in the IFM 2005-02 (*I*ntergroupe *F*rancophone du *M*yelome) trial. The study enrolled patients 65 years of age or younger with non-progressive MM who received consolidation treatment with lenalidomide after autologous stem-cell transplantation within the previous six months.

Patients (n = 614) were randomly assigned to receive consolidation treatment with lenalidomide 25 mg/day for 21 days per month for two months, followed by maintenance therapy with either placebo (in arm A) or lenalidomide 10 to 15 mg/day until relapse (in arm B).

The independent data and safety monitoring committee recommended that the trial be unblinded because of primary endpoint (progression-free survival) superiority for the lenalidomide arm (arm B) at the first prespecified interim analysis with a median follow-up of 24 months. In findings from the final analysis at a median follow-up of 34 months from randomization and 44 months from diagnosis, median progression-free survival was 42 months with lenalidomide and 24 months with placebo.

The reduction in risk (hazard ratio, 0.5) was highly significant ($P < 10^{-8}$). Although the benefit was found regardless of the pre-consolidation response level, initial beta$_2$-microglobulin level, the presence or absence of del 13, or type of induction regimen, multivariate analysis revealed four significant prognostic factors for increased progression-free survival:

- treatment with lenalidomide ($P < 0.0000001$)
- very good partial response after consolidation ($P = 0.001$)
- absence of del 13 ($P = 0.014$) (Its presence is generally a marker of reduced event-free survival, overall survival, and complete remission duration.)
- initial beta$_2$-microglobulin level of 3 or below ($P < 0.001$)

Four years after randomization, the rate of overall survival was 81% in both groups.

"A longer follow-up is required to appreciate the impact on overall survival," Dr. Attal said.

Lenalidomide was well tolerated overall. Definitive discontinuations of treatment attributed to adverse drug events were reported at 21% for lenalidomide and 15% for placebo. Higher rates of neutropenia, deep-vein thrombosis, and peripheral neuropathy were observed with lenalidomide.

Dr. Attal concluded, "Maintenance therapy with lenalidomide is superior to placebo."

Deferasirox (Exjade) Improves Liver Pathology In Beta-Thalassemia Patients With Transfusional Iron Overload

- Yves Deugnier, MD, University Hospital Pontchaillou, Rennes, France

Iron overload is associated with the development of liver fibrosis that may progress to cirrhosis. In beta-thalassemia patients with advanced cirrhosis and fibrosis, deferasirox (Exjade, Novartis) has been shown to reduce iron overload. Dr. Deugnier's study tested whether deferasirox would stabilize or improve necroinflammation and fibrosis in this patient population.

The study included data from two trials among patients with beta-thalassemia and transfusional hemosiderosis. One trial compared deferasirox with deferoxamine (Desferal, Novartis), and the other involved deferasirox only. Patients were receiving eight or more blood transfusions per year and had been treated for at least three years, up to five years. The deferasirox dose was 5 to 40 mg/kg per day based on the level of iron overload.

Fibrosis staging was performed according to the Ishak scale, ranging from 0 (no fibrosis) to 6 (cirrhosis, probable or definite). Liver inflammation was assessed according to the Ishak necroinflammatory grading system, with overall scores ranging from 0 to 18.[1]

The studies included 671 patients with beta-thalassemia. Among the 219 patients who had received deferasirox for at least three years, the mean age was 15.6 years (range, 2–49 years). Patients were stratified according to liver iron concentration (LIC) reduction success (group A) or failure (group B). Ishak necroinflammatory scores at baseline ranged from 0 to 8, with a mean of 2 (2.2 in group A, 1.6 in group B).

In 59 patients (26.9%), fibrosis was improved by two or more Ishak stages; 22 patients (10%) experienced worsening of fibrosis by two or more Ishak stages. Ishak necroinflammatory scores improved by a mean of –1.3 in all patients, with a mean absolute change of –1.5 in group A and a mean absolute change of –0.8 in group B.

Changes in Ishak grading did not correlate with changes in LIC. In addition, improvement or stabilization in liver fibrosis was observed in patients who met LIC success criteria and in those who did not.

"That suggests that the observed effects are independent of the drug's chelation effects," Dr. Deugnier said.

The data also suggest that up to five years of deferasirox treatment may reverse or stabilize fibrosis and improve liver

function in this population. Further study of deferasirox for the prevention of iron-induced tissue fibrosis in other organs is warranted.

Improved Survival With Eculizumab (Soliris) In Paroxysmal Nocturnal Hemoglobinuria

• Richard J. Kelly, MD, Consultant Hematologist and Honorary Senior Lecturer at St. James's University Hospital, Department of Haematology, Leeds, U.K.

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic and life-threatening hematopoietic stem-cell disorder characterized by uncontrolled activation of the complement system. As a consequence of subsequent chronic intravascular hemolysis, up to 35% of PNH patients die from serious clinical morbidities, including thromboembolism and chronic kidney disease, within five years of diagnosis.

Dr. Kelly reported a study among 79 consecutive patients who were treated with eculizumab (Soliris, Alexion) at his institution. Patients were eligible to enroll if they had received four or more transfusions for hemolytic disease within the previous 12 months, had experienced a thrombotic event, or had any other significant PNH complications.

Patients' mean age at diagnosis was 37 years (51% were men). The median lactate dehydrogenase (LDH) level, a measure of hemolysis, was 2,872 IU/L (up to 430 IU/L is within the normal range). LDH values in this study varied from 587 to 10,300 IU/L.

Under treatment, intravascular hemolysis was reduced, with the most recent average LDH measurement below 500 IU/L (range, 177–1,793 IU/L). A comparison of 12 months preceding therapy and 12 months after initiation of treatment revealed that the mean number of transfusions fell from 24.6 units (range, 4–52 units) to 14.6 units (range, 2–50 units), for a 74% reduction ($P = 0.03$). As of this writing, 40 of 61 patients evaluated (66%) had remained transfusion-independent for more than one year.

In patients receiving eculizumab, the rate of thrombotic events dropped to 0.8 events per 100 patient-years ($P < 0.001$). Before treatment, 21 patients had experienced 34 thrombotic events (5.6 events per 100 patient-years).

Twenty-one patients stopped primary anticoagulation and one patient stopped secondary anticoagulation without any occurrence of thrombosis (mean duration, 10.8 months). No deaths were attributed to PNH over the study period, and mortality rates after eight years among the 79 PNH patients were similar to those in age-matched and sex-matched controls (approximately 96% for both; $P = 0.46$).[2]

Dr. Kelly commented, "We've shown a normalization of survival in this study."

He cited earlier research among 80 patients treated for PNH between 1940 and 1970. That study had revealed a survival rate of approximately 53% for those patients at eight years, compared with a survival rate of about 97% for matched controls.[3] Some of the decrease in mortality rates since then, Dr. Kelly suggested, can be attributed to improvements in supportive care and better treatment of disease complications.

Samalizumab in Advanced B-Cell Chronic Lymphocytic Leukemia or Multiple Myeloma

• Daruka Mahadevan, MD, Arizona Cancer Center, University of Arizona College of Medicine, Tucson, Ariz.

Up-regulation of the cluster of differentiation 200 (CD200) on B-cell chronic lymphocytic leukemia (B-CLL) or multiple myeloma (MM) cells may contribute to immune evasion by tumors. Blocking CD200, preclinical data suggest, may enable a more efficient immune response against CD200-positive (CD200+) tumor cells.

Alexion's samalizumab, a first-in-class immunomodulatory humanized monoclonal antibody that blocks CD200, was tested in a phase 2/3 dose-escalation trial enrolling 26 patients with advanced B-CLL or MM. After receiving a single intravenous (IV) dose of samalizumab, patients were eligible for additional cycles of a single infusion every 28 days if they tolerated the first dose and if they exhibited at least stable disease. Twenty patients (77%) received multiple samalizumab cycles in dose cohorts ranging from 50 to 600 mg/m^2.

The most common adverse events were fatigue (in 50%), headache (in 20%), fever (in 20%), and rash (in 20%). Higher-grade adverse events (grades 3 to 5) that were considered possibly, probably, or definitely related to the study drug included anemia (in 8%), neutropenia (in 8%), thrombocytopenia (in 4%), reduced visual acuity (in 4%), respiratory syncytial virus infection (in 4%), muscular weakness (in 4%), and rash (in 4%). No severe or dose-limiting adverse cytokine reactions were reported, and the maximum tolerated dose was not reached.

Large reductions of 81% to 98% in peripheral CD200+ CD4+ T cells were reported in 19 of 20 patients in whom peripheral immune cells could be evaluated. In addition, 14 of 21 patients (67%) demonstrated a CD200 loss of 64% to 75% on B-CLL cells following the first dose of samalizumab.

Among 22 evaluable CLL patients, nine patients (41%) experienced at least a 10% reduction in bulky disease. A patient who had received 13 cycles (400 mg/m^2) achieved a confirmed partial response, with a maximum 71% reduction in bulky disease, as shown by computed tomography (CT), together with a reduction in absolute lymphocyte count of 50% or more while maintaining a neutrophil count of 1.5 x 10^9/L or greater. Among patients receiving samalizumab doses of 300 mg/m^2 or lower, CD200 loss was transient.

"The observed biological activities of samalizumab," Dr. Mahadevan said, "appear to be consistent with the predicted mechanism of action, suggestive of CD200 blockade."

The findings support the need for further study to explore other dosing regimens and tumor types.

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